Remarks

The amendments to the claims

Only two types of amendments are made to the claims: those correcting clerical errors and those directly addressing the claim construction raised by the examiner. Claims 92-99 and 112-117 were indicated as allowed in the final office action. Improper antecedent basis was subsequently noted in these claims and is corrected by the current amendment. This amendment was not made earlier because it was not noted earlier. It puts the claims in better form for allowance.

Each of claims 1, 5, 27, 37, and 61 are amended to recite "under an effective amount of low calcium ion concentration of" less than or equal to 500 micromolar. In addition, the phrase "the tissue" has been separated from the recitation of a calcium concentration. These amendments are to address the PTO's construction of the claims as previously describing the concentration of calcium in the tissue and as reading on the use of zero calcium. The recitation employed in the current amendment ("under an effective amount of low calcium ion concentration of") is the same as was added by examiner's amendment in the parent application which issued into U.S. Patent 6,376,471. These amendments were not made earlier because the PTO's construction of the claims was not provided earlier. It is respectfully submitted that these amendments provide new issues for search and do not insert new matter into the application.

The recitation of an effective amount of low calcium ion concentration of less than or equal to 500 micromolar is supported in the specification as filed. Paragraphs 16 and 17 of the application as published teach:

[0017] Low extracellular calcium ion concentration conditions also can be used to enhance vascular permeability. It has been found that transfer of administered nucleic acid to targeted cells is substantially enhanced under such conditions, which also is demonstrated in the Examples which follow. Low calcium concentration conditions may be readily provided, particularly by perfusing a low calcium ion concentration fluid through the vasculature of the tissue to which nucleic acid is administered. Suitable perfusate calcium ion concentrations may range from about 40 or 50 .mu.mol/L to about 500 .mu.mol/L, more preferably from about 50 .mu.mol/L to about 200 .mu.mol/L. A perfusate calcium concentration of about 50 .mu.mol/L is particularly preferred. Calcium ion (e.g. Ca.sup.2+) concentration also can be lowered through use of a suitable buffer such as a chelating agent, e.g. ethylenebis(oxyethylenenitrilo)tet- racetic acid (EGTA), ethylenediaminetetracetic acid (EDTA), or 1,2-bis-(2-aminophenoxy)ethane-N,N,N',N'-tetraacetic acid (BAPTA).

[0017] Additionally, while a low calcium ion concentration can enhance nucleic acid uptake, it is also important that a minimal calcium concentration be maintained during the gene transfer protocol, at least in many or some applications. If calcium-free or essentially calcium-free conditions (e.g. perfusate calcium ion concentration of about 10-20 .mu.mol/L or less) are employed, cell calcium channel selectivity may be destroyed which can result in cell death upon return to physiological calcium levels, particularly in the case of administration to myocytes.

The rejection of claims 1, 5, 27, 61, 66-72, 74, and 75 under 35 U.S.C. § 102(a)

Claims 1, 5, 27, 61, 66-72, 74, and 75 are rejected as anticipated by Fasano (WO 96/37196). Fasano is cited for teaching the use of a vascular permeability agent (zot protein) and a nucleic acid which is an attenuated virus. This rejection is respectfully traversed.

The office action urges that the recitation of a low calcium concentration described a characteristic of the tissue to which nucleic acid is being administered. The order of the claim terms in claim 1 has been changed to clarify that the nucleic acid is delivered under an effective low calcium concentration. In addition, the office action urges that the recited calcium concentration included zero. The claim language has been amended to recite the use of an

effective low concentration of calcium ion. This clarifies that some calcium ion is present. It is respectfully submitted that these amendments adequately distinguish the invention over the teachings of Fasano.

The rejection of claims 1, 5, 27, 61, 66-72, 74, and 75 under 35 U.S.C. § 102(e)

Claims 1, 5, 27, 61, 66-72, 74, and 75 are rejected as anticipated by Wolff (U.S. 6,265,387). Wolff is cited for teaching the use of a VEGF to enhance vascular permeability to a nucleic acid. However, Wolff does not teach the use of an effective low calcium concentration of less than or equal to 500 micromolar as required by each of claims 1, 5, 27, 61, 66-72, 74, and 75. Thus Wolff does not anticipate claims 1, 47 or 52.

The rejection of claims 1, 5, 27, 37, 61, 63, 64, 66-73, and 75 under 35 U.S.C. § 102(e)

Claims 1, 5, 27, 37, 61, 63, 64, 66-73, and 75 are rejected as anticipated by Ryan (US 2003/0195495 A1). Ryan is cited for teaching the use of a combination of VEGF, vascular permeability factor, and a nucleic acid encoding VEGF. However, Ryan does not teach the use of an effective amount of a low calcium ion concentration of less than or equal to 500 micromolar as required by each of claims 1, 5, 27, 37, 61, 63, 64, 66-73, and 75. Thus Ryan does not anticipate claims 1, 5, 27, 37, 61, 63, 64, 66-73, and 75.

The rejection of claims 1, 5, 27, 61-63, 66-87, 102, 105, and 108 under 35 U.S.C. § 103(a)

Claims 1, 5, 27, 61-63, 66-87, 102, 105, and 108 are rejected as obvious over Nabel (U.S. 5,328,470) taken with Wolff (U.S. 6,265,387), Epstein (U.S. 6,007,817), or Neufeld (U.S. 6,013,780). This rejection is respectfully traversed.

Nabel is cited for teaching a nucleic acid delivery kit comprising a catheter and DNA encoding a toxin. Wolff, Epstein, and Neufeld are each cited as disclosing a vascular permeability agent for enhancing the delivery of a bioactive molecule. The combination of these teachings would allegedly have been obvious.

To make a proper *prima facie* case of obviousness, the references must teach all elements of the rejected claims.

> To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

M.P.E.P. § 2143. Each of the rejected claims requires an effective low calcium ion concentration of less than or equal to 500 micromolar. None of the cited references teaches the use of such a low calcium ion concentration to enhance DNA delivery. Since the combination of references fails to teach all elements of the rejected claims, the rejection fails.

Withdrawal of this rejection is respectfully requested.

The rejection of claims 1, 27, 37-39, 76-91, 110, and 111 under 35 U.S.C. § 103(a)

Claims 1, 27, 37-39, 76-91, 110, and 111 are rejected as obvious over Ryan taken with Wolff, Epstein, or Neufeld. This rejection is respectfully traversed.

The rejection posits that it would have been obvious to modify the DNA delivery method of Ryan by employing a vascular permeability agent so as to enhance the delivery of DNA to target cells. Wolff, Epstein, or Neufeld are cited as teaching vascular permeability agents for

enhancing delivery of a bioactive molecule to target cells. However, the cited references alone or in combination do not teach the delivery of DNA or vascular permeability enhancing agents under conditions of an effective amount of low calcium ion as required by the claims. Thus the cited combination of references fails to each all elements of the claims, and thus the cited combination fails to present a *prima facie* case of obviousness.

Withdrawal of the rejection is respectfully requested.

Respectfully submitted,

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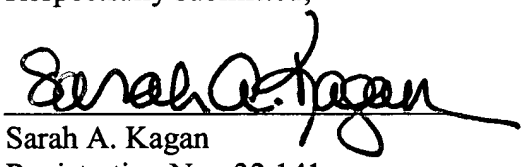
By: 

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